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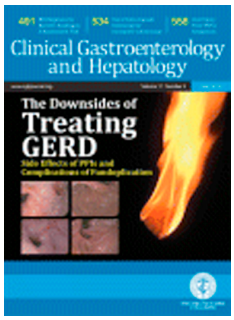

Monitoring Occurrence of Liver-Related Events and Survival by Transient Elastography in Patients With Nonalcoholic Fatty Liver Disease and Compensated Advanced Chronic Liver disease

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PII: S1542-3565(20)30908-3
DOI: https://doi.org/10.1016/j.cgh.2020.06.045
Reference: YJCGH 57319

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 17 June 2020

Please cite this article as: Petta S, Sebastiani G, Viganò M, Ampuero J, Wai-Sun Wong V, Boursier J, Berzigotti A, Bugianesi E, Fracanzani AL, Cammà C, Enea M, Grottes Md, Di Marco V, Younes R, Keyrouz A, Mazzola S, Mendoza Y, Pennisi G, Romero-Gomez M, Craxì A, de Ledinghen V, Monitoring Occurrence of Liver-Related Events and Survival by Transient Elastography in Patients With Nonalcoholic Fatty Liver Disease and Compensated Advanced Chronic Liver disease, *Clinical Gastroenterology and Hepatology* (2020), doi: https://doi.org/10.1016/j.cgh.2020.06.045.

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NUMBER OF FIGURES/SUPPLEMENTAL figures: 4/1

NUMBER OF TABLES/SUPPLEMENTAL TABLES: 2/2

LIST OF ABBREVIATIONS: NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; LSM: liver stiffness measurement; HCC: hepatocellular carcinoma.

CONFLICT OF INTEREST: SP has acted as speaker and/or advisor for Abbvie, Gilead and Intercept. GS has acted as speaker for Merck, Gilead, Abbvie, Novonordisk, served as an advisory board member for Merck, Gilead, Intercept and Novartis and has received unrestricted research funding from Merck and Theratec. GS is supported by a Junior 1 and 2 Salary Award from Fonds de Recherche Santé du Québec (FRQS) (#27127 and #267806) and research salary from the Department of Medicine of McGill University.

Author contributions: S Petta, G Sebastiani, M Viganò, J. Ampuero, M Romero-Gomez, VW Wong, J Boursier, A Berzigotti, E Bugianesi, AL Fracanzani, C Cammà, M des Grottes, V Di Marco, M Younes, A Keyrouz, S Mazzola, Y Mendoza, G Pennisi, A Craxì,

V de Ledinghen had full control of the study design, data analysis and interpretation, and preparation of article. All authors were involved in planning the analysis and drafting the article. The final draft article was approved by all the authors.

Abstract:

Background & Aims: Patients with advanced fibrosis related to nonalcoholic fatty liver disease (NAFLD) are at risk of developing hepatic and extrahepatic complications. We investigated whether, in a large cohort of patients with NAFLD and compensated advanced chronic liver disease, baseline liver stiffness measurements (LSMs) and their changes can be used to identify patients at risk for liver-related and extrahepatic events.

Methods: We performed a retrospective analysis of consecutive patients with NAFLD (n=1039) with a histologic diagnosis of F3–F4 fibrosis and/or LSMs>10 KPa, followed for at least 6 months, from medical centers in 6 countries. LSMs were made by FibroScan using the M or XL probe and recorded at baseline and within 1 year from the last follow-up examination. Differences between follow up and baseline LSMs were categorized as: improvement (reduction of more than 20%), stable (reduction of 20% to an increase of 20%), impairment (an increase of 20% or more). We recorded hepatic events (such as liver decompensation, ascites, encephalopathy, variceal bleeding, jaundice, or hepatocellular carcinoma [HCC]) and overall and liver-related mortality during a median follow-up time of 35 months (interquartile range, 19–63 months).

Results: Based on Cox regression analysis, baseline LSM was independently associated with occurrence of hepatic decompensation (hazard ratio [HR], 1.03; 95% CI, 1.02–1.04; P<.001), HCC (HR, 1.03; 95% CI, 1.00–1.04; P=.003), and liver-related death (HR, 1.02; 95% CI, 1.02–1.03; P=.005). In 533 patients with available LSMs during the follow-up period, change in LSM was independently associated with hepatic decompensation (HR, 1.56; 95% CI, 1.05–2.51; P=.04), HCC (HR, 1.72; 95% CI, 1.01–3.02; P=.04), overall mortality (HR, 1.73; 95% CI, 1.11–2.69; P=.01), and liver-related mortality (HR, 1.96; 95% CI, 1.10–3.38; P=.02).

Conclusions: In patients with NAFLD and compensated advanced chronic liver disease, baseline LSM and change in LSM are associated with risk of liver-related events and mortality.

KEY WORDS: NASH, steatohepatitis, cACLD, prognostic factor

Need to Know

Background: It is not clear whether, in patients with nonalcoholic fatty liver disease (NAFLD) and compensated advanced chronic liver disease, baseline liver stiffness measurements (LSMs) or their changes can be used to identify patients at risk for liver-related and extrahepatic events.

Findings: In patients with NAFLD and compensated advanced chronic liver disease, baseline LSM and change in LSM are associated with risk of liver-related events and mortality.

Implications for patient care: LSMs should be made at multiple timepoints in patients with NAFLD and compensated cirrhosis to monitor disease progression.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease worldwide with a prevalence of about 25% in general population [1,2]. The clinical relevance of NAFLD arises from the increased risk of developing both liver-related and extrahepatic complications [3-5].

Recent long-term natural history studies and a meta-analysis pooling available evidence demonstrated that the severity of liver fibrosis and especially the presence of advanced fibrosis -defined as stage F3 or F4 fibrosis- is the main driver of prognosis in NAFLD, being the main risk factor for developing not only liver-related events but also extrahepatic complications [6-8]. Along this line, noninvasive markers that can predict liver disease severity and outcomes in patients with NAFLD and advanced fibrosis are a major unmet need.

Liver stiffness measurement by FibroScan® is a noninvasive and widely available tool with validated diagnostic accuracy for advanced fibrosis in patients with NAFLD [9], and also used identifying patients at low risk for esophageal varices saving endoscopic screening [10], and lastly, increase over time of LSM predicted liver-related events in patients with chronic hepatic C [11].

Data about the accuracy of LSM in the prediction of events in NAFLD, and especially in patients with NAFLD and F3-F4 fibrosis, are scarce. With this in mind, we investigated whether, in a large cohort of patients with NAFLD and compensated advanced chronic liver disease (cACLD), LSM at baseline and its changes during follow-up, are accurate for the prediction of liver-related and extrahepatic events.

Patients and Methods

Patient Selection

Data from 1,039 patients and prospectively recruited at the first diagnosis of NAFLD with cACLD in 10 centers were retrospectively reviewed and analyzed.Inclusion and exclusion criteria were reported in supplemental material.

The study was carried out in accordance with the principles of the Helsinki Declaration, and with local and national laws. Approval was obtained from the hospital Internal Review Boards and their Ethics Committees, and written informed consent for the study was obtained from all patients.

Patient Evaluation (more data available in Supplemental material)

Clinical, anthropometric, biochemical and histological data were collected at the time of enrollment.

Follow-up visits, laboratory tests, ultrasound examination, esophageal gastroscopy, and management of both esophageal varices and HCC were performed as for guidelines [12-14].

During follow-up, liver-related and extrahepatic events were recorded. Liver-related events were categorized as either liver decompensation (occurrence of ascites and/or bleeding varices and/or encephalopathy and/or jaundice) or development of HCC. They were also evaluated for liver transplantation, as were patients who experienced LD, when indicated [14]. Extrahepatic events were categorized as either cardiovascular events (stroke, transient ischaemic attack, myocardial infarction, unstable angina) or extrahepatic

cancers. Evidence of extrahepatic events was provided by clinical charts from emergency areas and/or hospitalization. Death was also recorded and classified according to associated events (liver-related, including liver transplantion, or unrelated).

Transient elastography was performed with the FibroScan (Echosens, Paris, France) medical device, using the M or XL probes. In each center [15]. LSM was recoded within 3 months from blood tests and within 1 year from the last follow-up.

Statistics (more data available in Supplemental material)

To evaluate the occurrence of liver decompensation, HCC, cardiovascular events, extrahepatic cancers, and death, we included all consecutive patients who had at least 6 months of follow-up. Patients lost at follow-up (12% of the total population) were censored at the time of the last visit.

Continuous variables were summarized as mean ± standard deviation, and categorical variables as frequency and percentage. Delta LSM was defined as the difference between follow-up and baseline LSM and was categorized as <-20% (improvement), -20% to +20% (stable), and >+20% (impairment). This last criterion was used because values above and below 15% were considered as a normal variability of the procedure (as defined per the interquartile to median ratio of 30%). Covariates used for the multivariate model Cox were chosen based on their significance in univariate analysis ($p<0.10$). Variables in the final model with a P value of <0.05 were considered statistically significant. In order to take into account the between-center heterogeneity we fitted a random effects (frailty) Cox model.

Analyses were performed using SPSS (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.), and IDE software RStudio (version 3.4.1 of 2017-06-30) for the R (version 2.1) using the packages “timeROC” and “survival”.

Results

Clinical and Features and Liver Stiffness

Baseline characteristics of the 1039 patients with NAFLD and cACLD are shown in Table 1. The diagnosis of NAFLD was supported by histology in 550 cases (52.9%), and 7.2% of the population had Child Pugh A6 score.

Baseline median LSM value was 17.6 KPa. LSM was obtained by using M probe in 776 patients and XL probe in 263 patients; as expected mean BMI (34.4±6.5 vs 31.9±5.8; p<0.001) as well as the prevalence of obesity (75.2% vs 60.2%; p<0.001) were significantly higher in patients with LSM by XL probe compared to those with LSM by XL probe.

In a sub-group of 533 patients LSM within 1 year from the last follow-up and obtained by using the same probe used at baseline was available. These patients were older and had higher length of follow-up compared to those without LSM available at follow-up (Supplemental Table 1). Median delay between baseline and follow-up LSM was 37 months. In this group of patients, 53.3% experienced an improvement in follow-up LSM (<20% from baseline), 27.2% had stable values, and 19.5% had an impairment >20% in LSM values from baseline. Notably, among these three classes of patients, the presence of diabetes at baseline significantly predicted follow-up changes in LSM (56.8 %, 68.2% and 71.1%, respectively; p=0.01).

Liver-related and Extrahepatic Outcomes

Absolute numbers and the actuarial incidence rates for hepatic and extra-hepatic events are reported in Supplemental Table 2.

Prediction of Liver Decompensation by LSM

Independent variables predicting liver decompensation by Cox multivariate analysis included: age (HR 1.06, 95%CI 1.02-1.09, p=0.001), presence of Child Pugh A6 (HR 3.04, 95%CI 1.69-5.44; p<0.001), platelets (HR 0.98, 95%CI 0.97-0.98, p<0.001) and baseline LSM (HR 1.03, 95%CI 1.02-1.04, p<0.001) (Table 2). When including in the model PLT <150X10^3/mmc as categorical variable instead of PLT as a continuous variable, similar results were observed for LSM and PLT <150X103/mmc remained significant associated with liver decompensation (HR 7.83, 95%CI 2.51-21.3; p<0.001). The time dependent ROC of baseline LSM in predicting liver decompensation was 0.76, 95% CI 0.68-0-83. The threshold of 21 KPa indicating clinically significant portal hypertension (CSPH) [13] was confirmed independently associated with higher occurrence of liver decompensation (HR 3.71, 95%CI 1.89-6.78; p<0.001) (Figure 1).

In patients with LSM available at follow-up, Δ-LSM (HR 1.56, 95%CI 1.05-2.51, p=0.04) (Figure 2A), together with baseline LSM (HR 1.03, 95%CI 1.00-1.05, p=0.01), significantly predicted the occurrence of liver decompensation (Table 2). Notably, the model including Δ-LSM better predicted decompensation than the model without (H C-Index 0.86 vs 0.83, respectively; p=0.03). Figure 3A showed the crude rate of liver decompensation at the end of follow-up among delta LSM risk classes. When assessing the risk for liver decompensation in patients with or without CSPH by LSM, we found that delta LSM significantly predicted liver decompensation in patients without (HR 3.85, 95%CI 1.38-9.5, p=0.003) (Figure 4A and 4B), but not in those with CSPH (HR 1.45, 95%CI 0.93-2.21,

p=0.07). Moreover, in patients without baseline CSPH (LSM<21kPa), the rate of liver decompensation occurrence was 6.5% in those who reached at follow-up a LSM value suggestive of CSPH, and 2.3% in those where LSM did not reach this threshold (p=0.07).

Monitoring LSM do predict HCC occurrence

Female gender (HR 0.30, 95%CI 0.13-0.69; p=0.005), age (HR 1.06, 95%CI 1.01-1.09, p=0.007), and baseline LSM (HR 1.03, 95%CI 1.00-1.04, p=0.003) were independent variables by Cox-regression associated with the development of HCC (Table 2). When including in the model PLT <150X10^3/mmc as categorical variable instead of PLT as a continuous variable, similar results were observed for LSM and PLT <150X103/mmc was confirmed not sifnificatly associated with HCC (HR 0.99, 95%CI 0.35-2.72; p=0.95). The time dependent AUROC of baseline LSM in predicting HCC was clinically not acceptable (AUROC 0.66, 95%CI 0.49-0.83).

In patients with LSM available at follow-up, Δ-LSM (HR 1.72, 95%CI 1.01-3.02, p=0.04) (Figure 2B), but not baseline LSM (HR 1.02, 95%CI 0.98-1.05, p=0.27) significantly predicted the occurrence of HCC (Table 2). Notably, the model including Δ-LSM better predicted decompensation than the model without (H C-Index 0.84 vs 0.79, respectively; p=0.002). Figure 3B shows the crude rate of HCC at the end of follow-up among delta LSM risk classes.

LSM does not predict extra-hepatic events occurrence

Baseline LSM (HR 1.01, 95%CI 0.99-1.03, p=0.15) and Δ-LSM (HR 1.42, 95%CI 0.78-2.59, p=0.24) were not associated with occurrence of cardiovascular events at univariate Cox regression analysis.

Baseline LSM was associated with occurrence of extra-hepatic neoplasm (HR 1.02, 95%CI 1.00-1.04, p=0.03) in the univariate analysis but not at multivariate Cox regression analysis (HR 1.02, 95%CI 0.99-1.04, p=0.12). Δ-LSM was also not associated with the development of extrahepatic cancers (HR 0.78, 95%CI 0.42-1.45, p=0.44) (Table 3).

Δ-LSM predicted overall and liver-related mortality

Baseline LSM was not associated with overall mortality (HR 1.01, 95%CI 0.99-1.03, p=0.18) (Table 2). In patients with LSM available at follow-up, Δ-LSM (HR 1.73, 95%CI 1.11-2.69, p=0.01) (Figure 2C) and Child-Pugh A6 vs Child-Pugh A5 (HR 4.09, 95%CI 1.01-16.4, p=0.04), but not baseline LSM (HR 1.01, 95%CI 0.97-1.04, p=0.46) were independently associated with overall mortality (Table 2). Figure 3C showed the crude rate of overall death among delta LSM risk classes.

Age (HR 1.06, 95%CI 1.02-1.11, p=0.005), platelets (HR 0.99, 95%CI 0.98-0.99, p=0.01) and baseline LSM (HR 1.02, 95%CI 1.00-1.03, p=0.005) (time dependent ROC 0.76, 95% CI 0.60-0.91) were significant risk factors for liver-related death (Table 2). In patients with available delta LSM: age (HR 1.06, 95%CI 1.00-1.16, p=0.02) and Δ-LSM (HR 1.96, 95%CI 1.10-3.38, p=0.02) (Figure 2D), but not baseline LSM (HR 1.02, 95%CI 0.98-1.06, p=0.18) were independent variables predicting liver-related death (Table 2). Notably, the model including Δ-LSM better predicted liver-related death than the model without (H C-Index 0.80 vs 0.77, respectively; p=0.03). Figure 3D shows the crude rate of liver-related death among delta LSM risk classes.

Finally, nor baseline LSM (HR 1.00, 95%C.I. 0.97-1.03, p=0.75) neither Δ-LSM (HR 1.28, 95%C.I. 0.59-2.75, p=0.52) were associated with extrahepatic death at univariate Cox regression analysis.

Discussion

In the current study carried out in a large multicenter cohort of individuals with NAFLD and cACLD, and prospectively followed for a median time of 3 years, we found that baseline LSM accurately predicts liver decompensation and liver-related death, while changes overtime in LSM –delta LSM- can further stratify the risk of development of liver-related complications.

In our study, liver-related events were the most frequently observed complications (6.8% liver decompensation, 3.4% HCC), followed by cardiovascular events (3.4%) and extrahepatic cancers (2.4%). Moreover, we observed an overall death rate of 5.4%, mostly due to liver-related causes (3.2%). Long-term studies investigating the natural history of patients with biopsy-proven NAFLD reported cardiovascular events and extra-hepatic cancers as the two most frequent causes of death, even if the observed higher increase in the relative risk of death was showed for liver-related causes [16,17]. The occurrence rates of hepatic and extrahepatic outcomes that we reported differ with respect to other studies [16,17], perhaps due to the selection of a population with cACLD, already committed for a higher risk of liver-related complications.

Baseline LSM values accurately predicted the occurrence of liver decompensation. This result was maintained after adjusting for the severity of liver disease (Child-Pugh A5 versus A6) and for surrogate markers of portal hypertension (platelet count). Notably, we found that when using the LSM threshold of 21 KPa, validated as indicating a high risk for CSPH [13], also in a setting of patients at risk for decompensation because of with cACLD, we identified two different populations, one at low (2%) and another at high (14%) risk of hepatic decompensation. Our study agrees with recent evidence that higher baseline LSM values can predict the development

of liver-related events in NAFLD [18]. However this last study included a smaller cohort of patients with NAFLD and advanced liver disease, did not consider separately liver decompensation and HCC, and did not explore the clinical utility of LSM in the at high risk setting of patients with severe fibrosis/compensated cirrhosis [19]. Another relevant finding of our study is that delta LSM can further stratify the risk for liver decompensation. We demonstrated a progressive increase in the probability of hepatic decompensation from 3.8% in patients who improved LSM of at least 20%, to 6.2% in stable kPa -20% to 20%, and further to 14.4% in those who impaired LSM >20% from baseline. Notably, when stratifying patients according to the risk of CSPH, we showed that while in patients at high CSPH risk, the delta LSM did not longer predict hepatic decompensation, its predictability was maintained in patients at low risk of CSPH at baseline, indeed, LSM improvement was associated with no hepatic decompensation, while the risk progressively increased to 3.2% in stable stiffness, and further to 10% when LSM impaired.

Baseline LSM values were independently associated with the occurrence of HCC, even if the overall accuracy was not clinically acceptable. Consistent with our results, a recent study in NAFLD patients at any stage of liver fibrosis showed a significant link between HCC risk and LSM values, but the authors cannot find accurate specific cut-offs to predict HCC occurrence [18]. ∆-LSM but not baseline LSM, showed an independent association with the risk of developing HCC: from 2.4% in improvement to 3.4% in stable and further to 6.7% when impaired stiffness.

After adjusting for confounders, we found an independent association between baseline LSM and liver-related but not overall mortality. The good prediction ability of baseline LSM for liver-related mortality was also demonstrated in two independent studies focusing on patients with clinical diagnosis of NAFLD at any stage of liver fibrosis [19,20]. Regarding the association between overall

mortality and baseline LSM, some study reported a lower diagnostic performance of baseline LSM respect to the prediction of liver-related mortality [19], while some other study showed a good performance also for predicting overall mortality [18]. Differences in the baseline prevalence of liver disease severity and, consequently in the incidence of hepatic and extrahepatic events leading to mortality, can explain the observed differences among studies. Notably, when in our cohort we considered delta LSM, we found that it can significantly stratify the risk of both overall and hepatic death, suggesting that impairment in liver disease severity can also increase the risk for extra-hepatic mortality as also suggested in a recent meta-analysis [6].

We observed that 53% of patients with paired LSM had LSM improvement defined as LSM reduction >20% from baseline, this percentage being higher than that reported in literature for at least 1 stage fibrosis regression in patients with paired liver biopsies [21]. However it is well known in literature that LSM in NASH is not only expression of hepatic fibrosis but it is also directly associated with ALT levels –as expression of liver inflammation- and BMI [22]. Consistently, the reduction of at least 20% that we observed in about half of NASH patients with paired LSM can be considered as a surrogate of improvement in liver damage (fibrosis and/or inflammation) and/or in its risk factors like obesity. Unfortunately, this is only a plausible hypothesis because data on ALT and BMI at follow-up were not available.

From a clinical point of view our study suggests that in a setting of patients with NAFLD at high risk of hepatic complications because of cACLD, a dynamic and integrated evaluation of baseline LSM together with delta LSM can help in stratifying the risk of liver decompensation, while delta LSM alone, not baseline, could better stratify the risk of HCC occurrence and of both hepatic and extra-hepatic death (Supplemental Figure 1). We can hypothesize that LSM impairment overtime can be expression of an impairment in liver

disease severity in terms of fibrosis, inflammation, steatosis and portal hypertension [10,22,23]. Notably, we found that the presence of diabetes at baseline indicates a higher risk of delta LSM impairment. This data agree with available literature identifying diabetes as a risk factor for liver disease progression and liver-related complications [24-26].

In our study we did not find any significant independent association between neither baseline nor delta LSM and occurrence of cardiovascular events and extra-hepatic cancers. Our results agree with data reported in a cohort of NAFLD patients at any stage of liver damage, where baseline LSM was not associated with extra-hepatic cancers while showing a statistically significant association but not clinically acceptable accuracy for cardiovascular event development [18].

The main limitation of this study lies in the potentially limited external validity of the results for different populations and settings. Our study included a large cohort of patients with NAFLD and advanced liver fibrosis followed at tertiary care centers. Another relevant limitation is the retrospective design of the study, and the not standardized protocol of LSM follow-up potentially leading to a selection bias. The lack of data about follow-up clinical variables including biochemical tests like ALT-expression of liver inflammation-and BMI could further limit the interpretation of our results. In particular, weight loss leading to BMI reduction is known to be associated with NASH resolution and fibrosis improvement in NAFLD patients [27], and ALT normalization has been identified as a predictor of histological improvement in NASH [28]; consistently the lack of data about the effect of ALT and BMI changes on liver-related outcomes can limit the strength of our results about LSM changes and prognosis in NAFLD population. In fact, delta LSM could be expression of factors also influencing the natural history of liver disease such as weight changes, transaminases fluctuations, or reflecting progression of liver disease such as changes in platelet count and in liver function indexes. Finally, hidden alcohol intake at

baseline and during follow-up, and lack of data about baseline and follow-up use of non-selective betablockers, could further affect the observed results.

In conclusion, this study conducted in a multicenter cohort of patients with NAFLD and cACLD showed that an integrated assessment of baseline and/or delta LSM can help in stratifying the risk of development of liver-related complications and of both hepatic and overall mortality. These data, if further validated, could help personalize prognosis and follow-up in NAFLD with cACLD.

Legends

Figure 1. Occurrence of liver decompensation in the entire cohort of NAFLD patients with cACLD according to LSM value of 21 KPa indicating a high risk of CSPH. p value by log-rank.

Figure 2. Delta LSM risk classes and occurrence of liver-related events and death in the entire cohort of NAFLD patients with cACLD. (A) Liver Decompensation; (B) Hepatocellular carcinoma; (C) Overall death; (D) Liver-related death. p value by log-rank.

Figure 3. Crude rate of liver-related events and death at the end of follow-up according to delta LSM risk classes in the entire cohort of NAFLD patients with cACLD. (A) Liver Decompensation; (B) Hepatocellular carcinoma; (C) Overall death; (D) Liver-related death. p value by log-rank.

Figure 4. Occurrence (A) and crude rate (B) of liver decompensation in the sub-group of patients with NAFLD and without CSPH by LSM (LSM <21 KPa).

Supplemental Figure 1. Proposed Algorithm to stratify the risk of complications in patients with cACLD by using baseline and delta LSM.

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Table 1. Baseline Demographic, Metabolic, Laboratory and Instrumental Features of patients with NAFLD and cACLD.

	NAFLD with cACLD N=1039
Mean Age – years	60.3 ± 10.7
Male Gender	56.3 %
Mean BMI – Kg/m^2	32.4 ± 6.1
Obesity -BMI≥30Kg/m^2	66.3%
ALT – IU/L	62.8 ± 50.3
PLT – 10^3/mmc	186.6 ± 74.3
Total Bilirubin – mg/dL	0.7±0.4
INR	1.0±0.2
Albumin – g/L	4.2 ± 0.4
Blood Glucose – mg/dL	128.0 ± 80.4
Total Cholesterol – mg/dL	171.4 ± 53.5
Triglycerides – mg/dL	150.5 ± 99.4
Type 2 Diabetes	60.8 %
Arterial Hypertension	68.2%
LSM– Kpa (Median and 1st/3rd quartiles)	17.6 (13.1/26.1)
Child A5/A6	92.8%/7.2%
Time of follow-up – months (Median and 1st/3rd quartiles)	35 (19/63)

Abbreviations: BMI, body mass index; PLT, platelet; ALT, alaninoaminotransferase; LSM, liver stiffness measurement. Data are given as mean ± standard deviation, or as percentage of cases (%).

Group	Variable	Adjusted Model HR (95% C.I.) p value	Adjusted Model HR (95% C.I.) p value

Table 2. Cox regression analysis of factors associated with liver events and liver-related death in the entire cohort of NAFLD and cACLD.

		Entire Cohort (N=1039)	Cohort with Availability of Follow-up LSM (N=533)
Liver Decompensation	**Age – years**	1.06 (1.02-1.09) 0.001	1.06 (1.00-1.11) 0.02
	Child Pugh A6	3.04 (1.69-5.44) <0.001	1.63 (0.49-5.28) 0.42
	PLT - 10^9/mmc	0.98 (0.97-0.98) <0.001	0.98 (0.97-0.98) <0.001
	Baseline LSM -KPa	1.03 (1.02-1.04) <0.001	1.03 (1.00-1.05) 0.01
	Delta LSM -KPa	-	1.56 (1.05-2.51) 0.04
		Entire Cohort (N=1039)	**Cohort with Availability of Follow-up LSM (N=533)**
Hepatocellular Carcinoma	**Female gender**	0.30 (0.13-0.69) 0.005	0.28 (0.08-0.85) 0.02
	Age – years	1.06 (1.01-1.09) 0.007	1.04 (0.98-1.10) 0.13
	PLT- 10^9/mmc	1.00 (0.99-1.00) 0.25	1.00 (0.99-1.00) 0.73
	Child Pugh A6	0.80 (0.25-2.49) 0.71	3.25 (0.80-13.1) 0.09
	Baseline LSM -KPa	1.03 (1.00-1.04) 0.003	1.02 (0.98-1.05) 0.27
	Delta LSM -KPa	-	1.72 (1.01-3.02) 0.04
		Entire Cohort (N=1039)	**Cohort with Availability of Follow-up LSM (N=533)**
Cardiovascular Event	**Female gender**	0.46 (0.21-0.96) 0.04	0.18 (0.03-0.78) 0.02
	Age – years	1.03 (0.99-1.07) 0.08	1.06 (0.99-1.13) 0.07
	Arterial Hypertension	2.16 (0.81-5.72) 0.12	3.03 (0.67-13.6) 0.15
		Entire Cohort (N=1039)	**Cohort with Availability of Follow-up LSM (N=533)**
Extra-hepatic Cancer	**Age – years**	1.04 (0.99-1.08) 0.06	1.04(0.98-1.09) 0.19
	Child Pugh A6	1.78 (0.51-6.07) 0.36	1.12 (0.13-9.46) 0.92
	Baseline LSM -KPa	1.02 (0.99-1.04) 0.12	1.01 (0.97-1.04) 0.756
		Entire Cohort (N=1039)	**Cohort with Availability of Follow-up LSM (N=533)**
Overall Death	**Female gender**	0.62 (0.33-1.14) 0.13	0.60 (0.27-1.33) 0.21
	Age – years	1.04 (1.01-1.08) 0.01	1.04 (0.99-1.08) 0.09
	BMI –Kg/m^2	0.91 (0.84-0.97) 0.006	0.93 (0.85-1.02) 0.12
	Child Pugh A6	4.22 (1.83-9.71) <0.001	4.09 (1.01-16.4) 0.04
	PLT - 10^9/mmc	1.00 (0.99-1.00) 0.21	1.00 (0.99-1.00) 0.78
	Baseline LSM -KPa	1.01 (0.99-1.03) 0.18	1.01 (0.97-1.04) 0.46
	Delta LSM -KPa	-	1.73 (1.11-2.69) 0.01
		Entire Cohort (N=1039)	**Cohort with Availability of Follow-up LSM (N=533)**
Liver-related Death	**Age – years**	1.06 (1.02-1.11) 0.005	1.06 (1.00-1.16) 0.02
	Child Pugh A6	1.71 (0.60-4.13) 0.36	2.12 (0.31-11.5) 0.49
	PLT - 10^9/mmc	0.99 (0.98-0.99) 0.01	0.99 (0.98-1.00) 0.34
	Baseline LSM –Kpa	1.02 (1.00-1.03) 0.005	1.02 (0.98-1.06) 0.18

	Delta LSM –Kpa	-	1.96 (1.10-3.38) 0.02

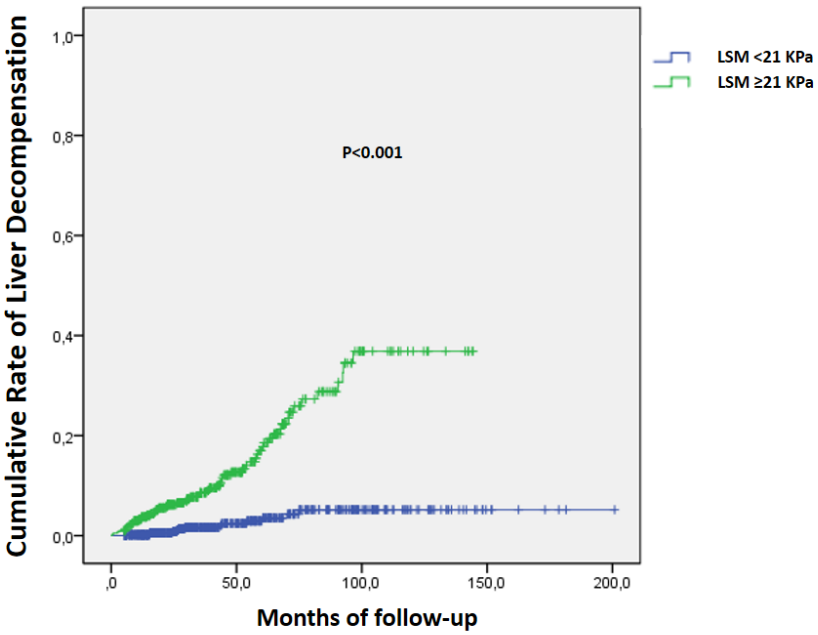

Figure 1

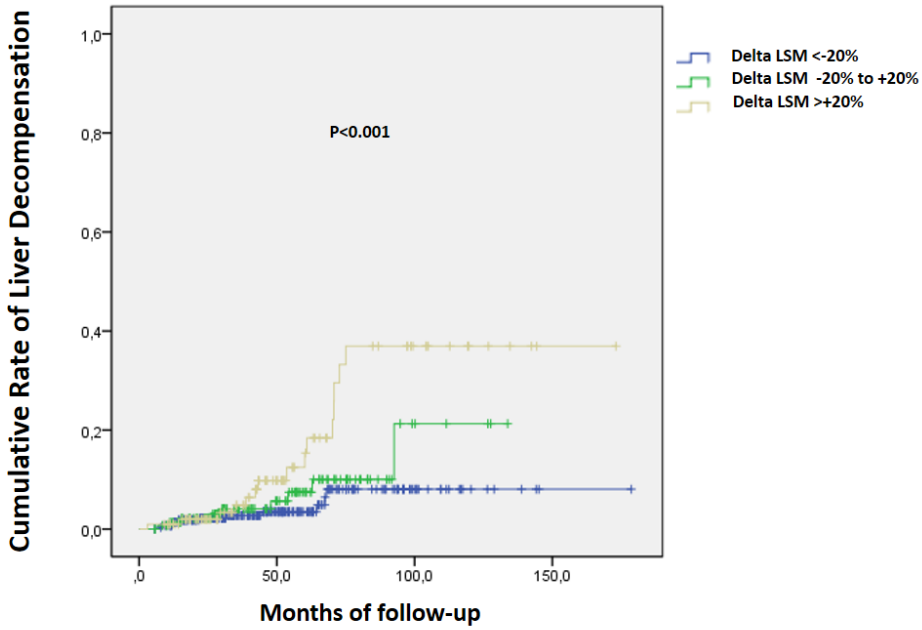

Figure 2A

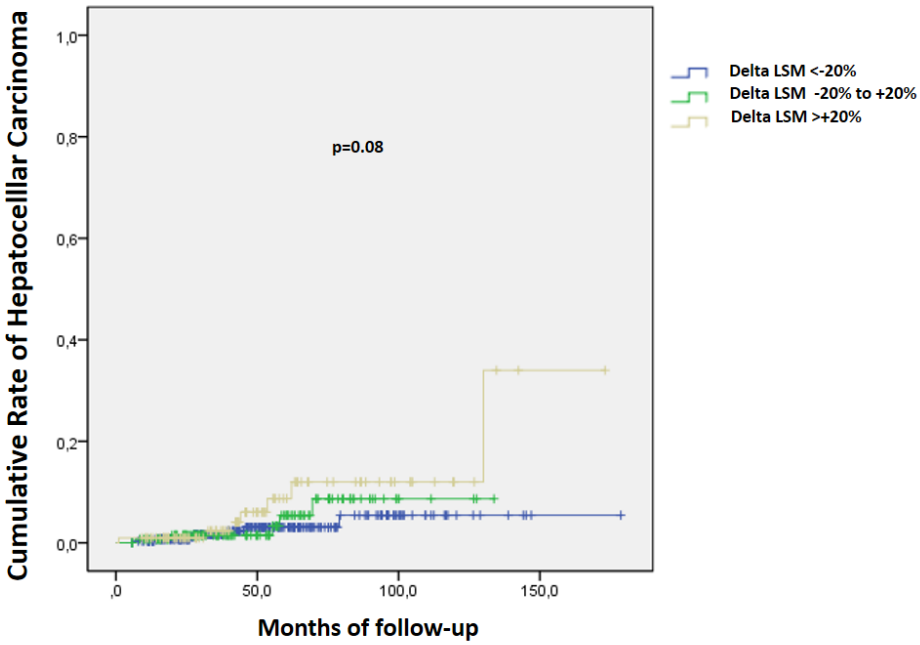

Figure 2B

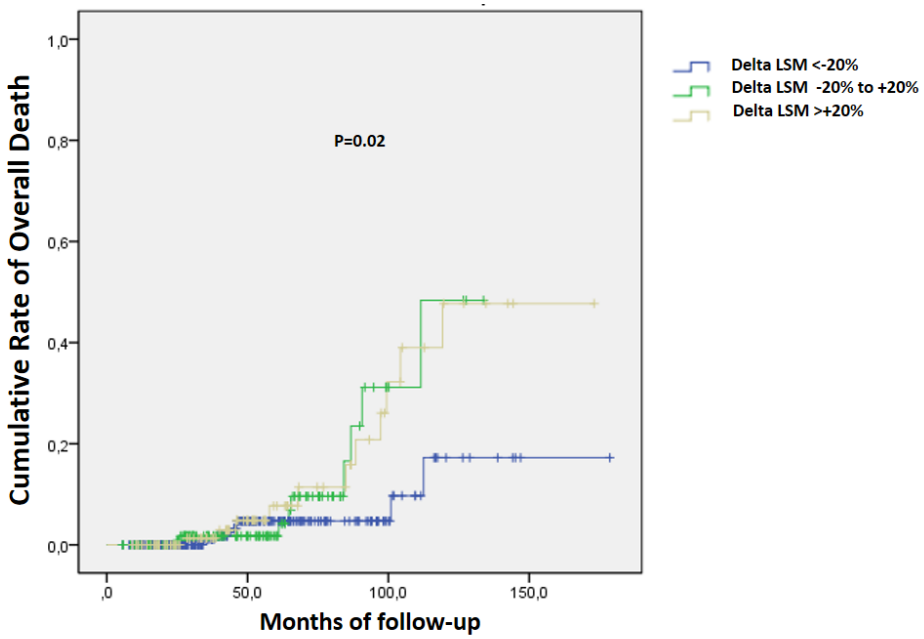

Figure 2C

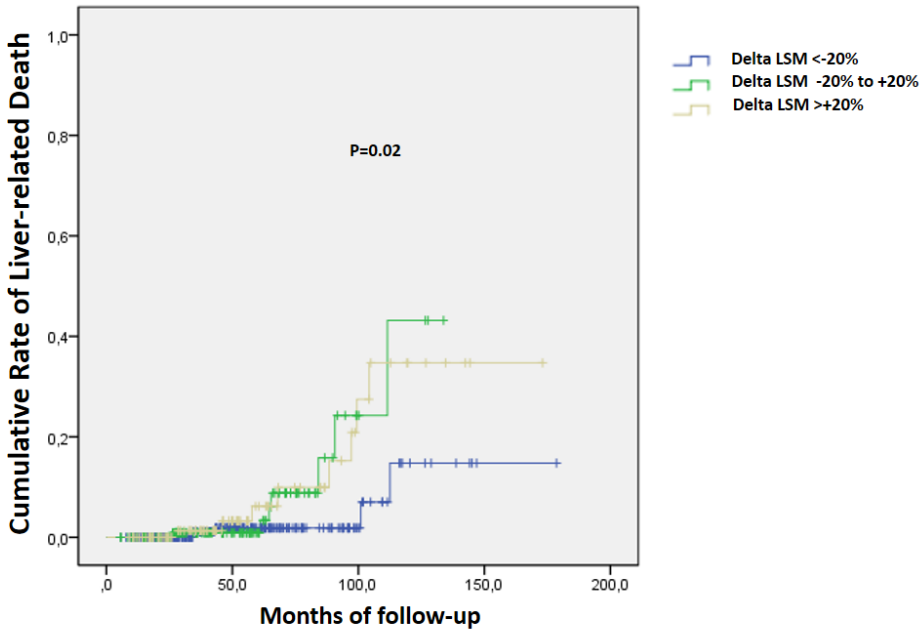

Figure 2D

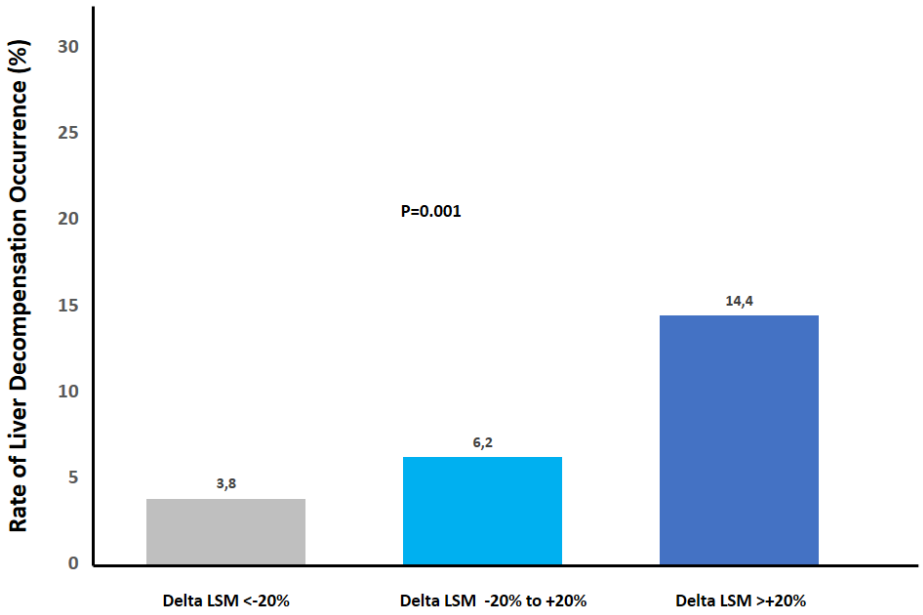

Figure 3A

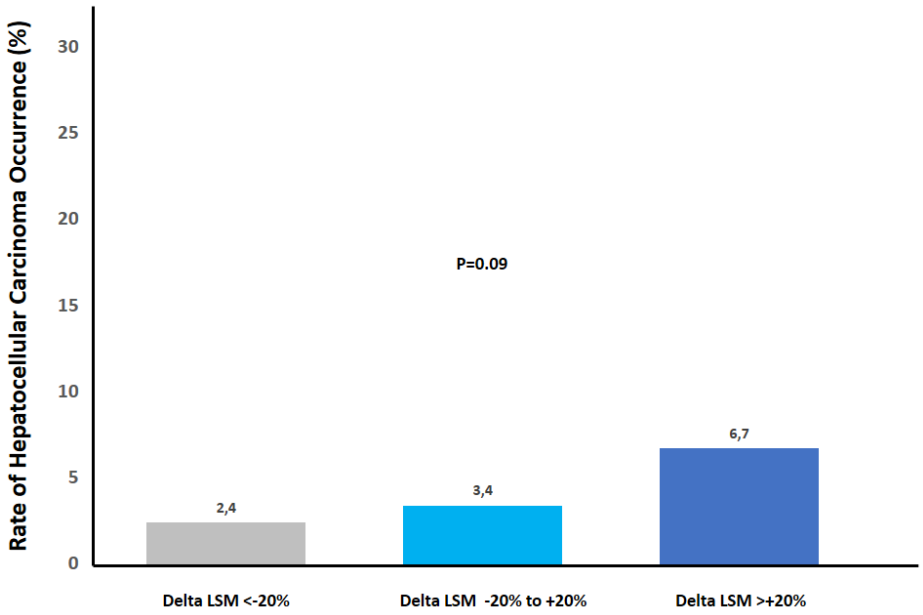

Figure 3B

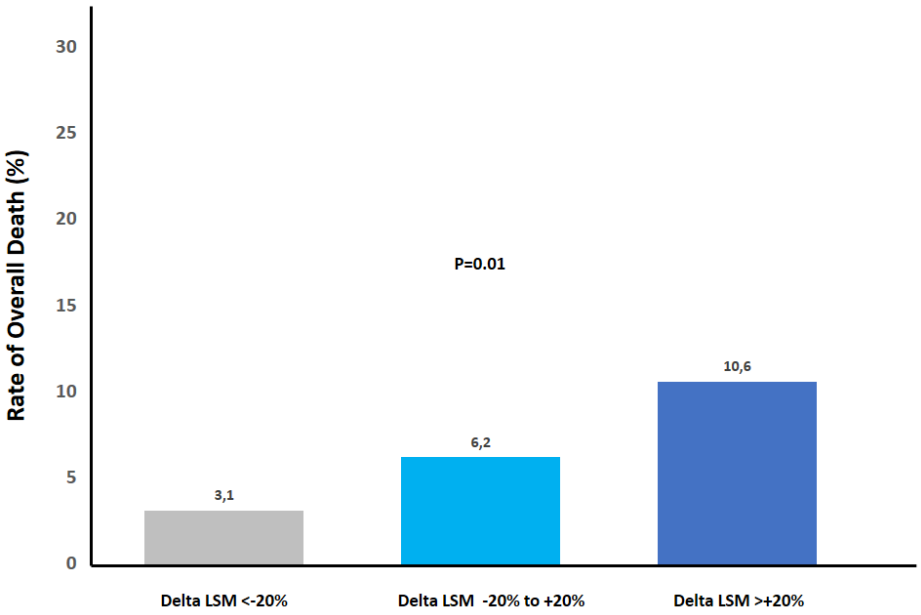

Figure 3C

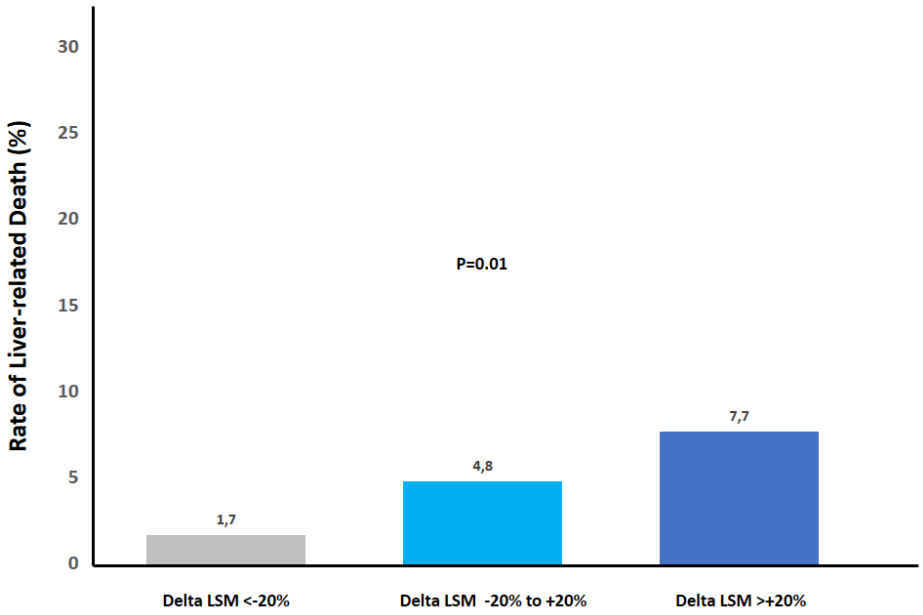

Figure 3D

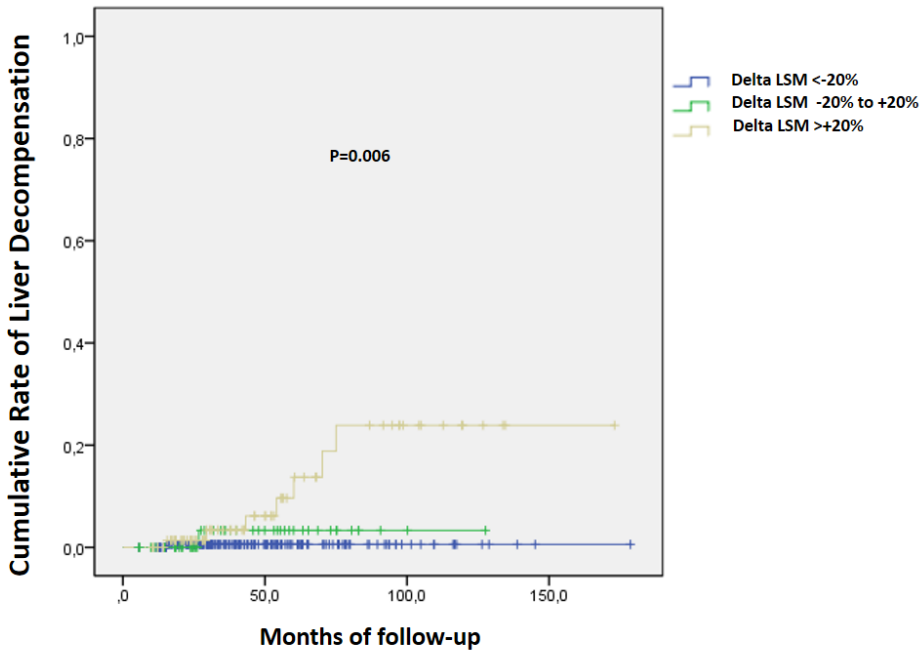

Figure 4A

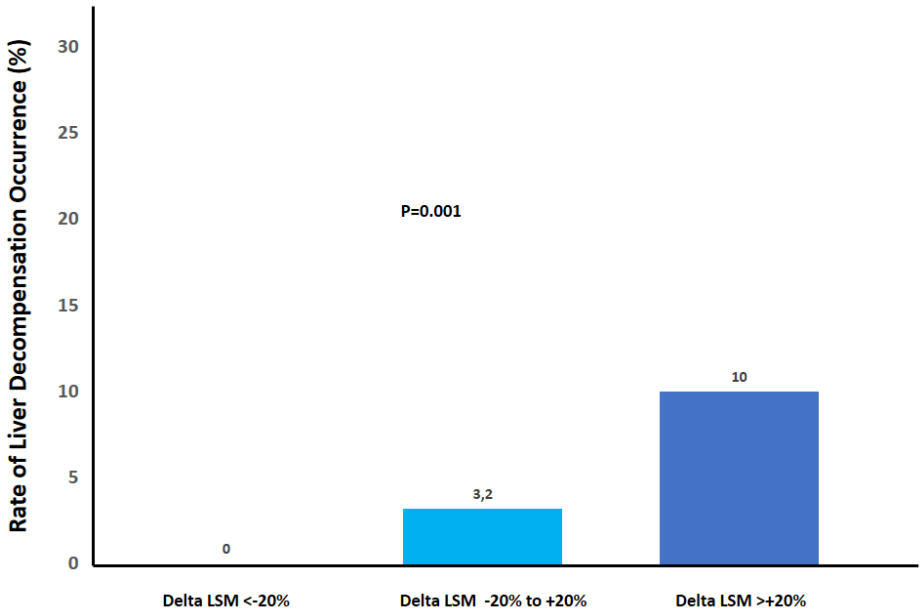

Figure 4B

What You Need to Know

Background: It is not clear whether, in patients with nonalcoholic fatty liver disease (NAFLD) and compensated advanced chronic liver disease, baseline liver stiffness measurements (LSMs) or their changes can be used to identify patients at risk for liver-related and extrahepatic events.

Findings: In patients with NAFLD and compensated advanced chronic liver disease, baseline LSM and change in LSM are associated with risk of liver-related events and mortality.

Implications for patient care: LSMs should be made at multiple timepoints in patients with NAFLD and compensated cirrhosis to monitor disease progression.